Remarks

In view of the above amendments and the following remarks, reconsideration of the outstanding office action is respectfully requested.

By the above amendments, claims 4–6, 21, and 41 are amended. Support for the amendments can be found in the specification at, *e.g.*, page 2, lines 1–16 and 25–31, page 7, lines 21–28, and Figure 1. Claims 1–8, 11–19, 21–29, 34–43, and 46–48 are pending, with claims 1–3, 11–19, 22–25, 34–40, 42–43, and 46–38 being withdrawn. No new matter has been added.

The objection to claim 4 is respectfully traversed in view of the above amendments. In particular, claim 4 has been amended to clearly recite that the DNA includes (i) the 5′ component, (ii) the 3′ component or (iii) both. Accordingly, the objection to claim 4 is inappropriate and should be withdrawn.

The objection to claim 21 is respectfully traversed in view of the above amendments. In particular, claim 21 has been amended to replace "comprises" with "is" as suggested by the U.S. Patent and Trademark Office ("PTO"). Accordingly, the objection to claim 21 is inappropriate and should be withdrawn.

The rejection of claims 4, 5, 7, 8, 21, 26, 28, 32, and 41 under 35 U.S.C. § 103(a) for obviousness over Alli et al., "Pharming Vaccines for Hepatitis and Cytomegalovirus: Towards the Development of Multivalent and Subunit Vaccines for Oral Delivery of Antigens," *Phytochem. Rev.* 1:55–66 (2002) ("Alli"), in view of Hirahara et al., "Preclinical Evaluation of an Immunotherapeutic Peptide Comprising 7 T-cell Determinants of Cry j 1 and Cry j 2, the Major Japanese Cedar Pollen Allergens," *J. Allergy Clin. Immunol.* 108:94–100 (2001) ("Hirahara") is respectfully traversed.

Claim 32 was previously canceled. The rejection of claims 4, 5, 7, 8, 21, 26, 28, and 41 is respectfully traversed in view of the above amendments, for the following reasons.

Alli discusses a plant based high fidelity vaccine production system being developed with emphasis on producing antigens capable of being orally delivered in multivalent or subunit plant packets. Alli states that plant-based edible vaccines may provide an attractive, safe, and inexpensive alternative to conventional vaccine production. Page 61, Figure 3, of Alli

has been cited by the PTO for teaching the production of a viral glycoprotein in rice seeds using the glutelin (Gt3) promoter and the Gt3 signal peptide.

Hirahara has been cited for teaching the recombinant production of peptides that are allergen-specific T-cell epitopes from the Cry j 1 and Cry j 2 proteins from Japanese cedar pollen.

The PTO has taken the position that it would have been obvious to one of ordinary skill in the art to modify th vaccine production system of Alli to express the recombinant Cry j 1 or Cry j 2 allergens of Hirahara to yield an edible, plant-based immunotherapeutic for the treatment of Japanese cedar pollinosis.

Applicants respectfully disagree, both with the PTO's characterization of the prior art teachings and with the PTO's conclusions of obviousness. With regard to the former, Applicants point out that, contrary to the PTO's assertion, Alli does **not** "specifically teach the production of a viral glycoprotein in ***rice seeds*** using the glutelin (Gt3) promoter and the Gt3 signal peptide …." *See* Office Action, at 5–6 (citing Alli, at 61 fig.3) (emphasis added). Rather, the referenced teaching involves the transformation of ***tobacco*** seeds (*see* Alli, at 61 fig.3, etc.). In addition, the Alli protocol utilized the 906-aa glycoprotein B (gB) polypeptide endogenous to human cytomegalovirus (HCMV), an entity that is both structurally and functionally distinct from Hirahara's 96-aa synthetic hybrid peptide comprising 7 T-cell determinants of Cry j 1 and Cry j 2. Given these fundamental distinctions, coupled with the high level of unpredictability associated with the recombinant arts, Applicants respectfully submit that the two teachings may not be routinely combined with the degree of predictability required to support a finding of obviousness. Furthermore, one of ordinary skill in the art could not have reasonably foreseen the unexpected results arising from the presently claimed invention that undermine and/or rebut the PTO's suggestion of "obviousness".

On the issue of unexpected results, we note that the PTO dismissed the previously filed arguments on the following grounds.

(a) The pending claims do not require any particular amount of accumulation; accordingly, Applicants' argument that "high accumulation" cannot be predicted from the prior art is not found persuasive. Office Action, at 7.

(b) "T-cell epitopes are small linear peptides with no important tertiary structure"; accordingly, it is neither surprising nor unexpected that a T-cell epitope can be heated without destroying its antigenicity. *Id.* at 7–8.

Thus, it appears that the PTO's challenge is not to the validity of the unexpected results but to whether these results are commensurate in scope with the pending claims. However, the present claims, as amended, relate to methods for accumulating ***high levels*** of a hybrid peptide in a plant, where the hybrid peptide ***comprises seven or more sequentially linked allergen-specific T-cell epitope peptides***. Such amendments render moot the PTO's concerns and negate the suggestion of obviousness.

In particular, with respect to the PTO's ground (a) regarding the failure of the claims to specify "high accumulation," Applicants note that the claims as amended herewith require accumulation of "high levels" of a hybrid peptide in a plant (claims 4, 5, 7, 8, 21, 26, 28, and 41), and more particularly in an edible portion thereof (claims 4, 7, 8, 21, and 41). One of ordinary skill in the art, when construing the claims in light of the teachings of the specification and in the context of edible plant vaccines, will understand that the term "high level" implies accumulation sufficient "to treat allergic reactions derived from such allergens by oral intake through the immune tolerance mechanism" (*see* Present Application, at 29–31), for example 30 μg of peptide per 20 mg of edible plant product (*see* Present Application, at 3:4–6) or on the order of 4% of the total seed protein (*see* Present Application, at 22:7–13, fig.1). This stands in stark contrast with the teachings of Alli, wherein the expressed protein represented 1.2 μg/mg total soluble protein, equivalent to 5 μg/mg dry seeds, with remaining seed protein (over 99.8%) presumed to be similar to non-transformed seed protein (*see* Alli, at p.60 col.2 ll.13–18). In fact, Applicants themselves observed that embodiments lacking the signal sequence present a maximum accumulation of 16 μg, corresponding to 1.1% of the total seed protein (*see* Present Application, at 22:14–20, fig.2). As noted previously, one of ordinary skill in the art cannot reasonably predict expression and accumulation of artificial genes *a priori.* Nor could one have predicted the elevated accumulation of the claimed hybrid peptide exclusive to the edible seed component. Recall that, although the hybrid peptide is transcribed in the leaves, stem, and root of other plants, it surprisingly does not accumulate there and is quickly degraded, even in rice leaves.

Accordingly, Applicants respectfully submit that the requisite high level accumulation in a plant, particularly an edible portion thereof, of an artificial hybrid peptide comprised of sequentially linked T-cell epitopes cannot be predicted from the teachings of Alli and/or Hirahara, particularly those pertaining to the expression of large, endogenous whole antigens. Thus, Applicants reiterate that the teachings of the cited references not only fail to provide a sufficient basis for a reasonable expectation of success but also fail to account for Applicants' unexpected success.

With respect to the PTO's ground (b), Applicants note that the hybrid peptide of claims 4, 5, 7, 8, 21, 26, 28, and 41, as amended herein, comprises seven or more sequentially linked allergen-specific T-cell epitope peptides, which cannot be fairly characterized as "a short linear peptide" and in fact likely falls within the 100–200 amino acid range previously mentioned. As noted in the instant specification at page 7, lines 19–21, epitope peptides generally "comprise about 10 to 25, more preferably 12 to 19 amino acid residues". Thus, one would expect the 7+ epitope-containing hybrid peptide of the present claims to be on the order of 70 to 175, more preferably 84 to 133, amino acids in length.

As noted previously, prior to the present invention, no one had introduced peptides on the order of 100–200 amino acid residues like the disclosed hybrids of Japanese cedar pollen allergen Cry j1 or Cry j2 and managed to successfully and stably accumulate such a long peptide. Thus, accumulation alone represents a substantial surprising discovery. However, embodiments of the present invention additionally possess surprising thermostability, with no alteration in the T-cell epitope-linked peptide being observed before and after a 20-minute heat treatment of transformant seeds and even being stably present after cooking the rice. *See* Present Application, at 3:14–16, Ex. 5, fig.8. In the case of an allergy vaccine (*e.g.*, a T-cell epitope), thermostability is indeed a major discovery. Unlike Alli's transformed seeds, which must be ground to permit oral delivery of the pathogenic antigens harbored therein, Applicants' invention permits oral delivery of allergens in a more conventional and indeed gastronomically acceptable way. Furthermore, the vaccine of the present invention has the characteristic of accumulating mostly in protein granules I (PB-I) where prolamin accumulates. This accumulation site is important in that it makes it hard for the vaccine to be digested by stomach acids and therefore facilitates efficient delivery to immune tissues of the intestinal canal.

In sum, Applicants submit that it is indeed surprising that a hybrid peptide as presently claimed could be successfully accumulated at high levels and possess the disclosed thermostability.

As demonstrated above, one of ordinary skill in the art would not have had a reasonable expectation of success in carrying out the presently claimed methods due to the high degree of unpredictability in the art. Further, the presently claimed methods provide a surprising and substantial superiority over the methods of the cited references.

For all of the above reasons, the rejection of claims 4, 5, 7, 8, 21, 26, 28, 32, and 41 for obviousness over Alli and Hirahara is improper and should be withdrawn.

The rejection of claims 6, 27, and 29 under 35 U.S.C. § 103(a) for obviousness over Alli in view of Hirahara, U.S. Patent No. 5,990,384 to Bagga et. al. ("Bagga"), and Kim et al., "Improvement of Nutritional Value and Functional Properties of Soybean Glycinin by Protein Engineering," *Protein Engin'g* 3:725–31 (1990) ("Kim") is respectfully traversed in view of the above amendments.

Bagga has been cited for teaching a stable protein that is expressed in a plant as a fusion protein comprising a zein protein and an operably linked protein or peptide.

Kim has been cited for teaching that modifications of glycinin can be rationally designed by identifying the variable domains and making insertions in the cDNA regions corresponding to variable domains.

The PTO's position is that it would have been obvious to further modify the Alli-Hirahara system to use the storage proteins taught by Bagga and Kim as carriers for the antigenic Cry j peptides, including embodiments wherein the antigenic Cry j peptides are inserted into a variable region of the storage protein. Applicants respectfully disagree, for substantially the reasons noted above in response to the rejection of claims 4, 5, 7, 8, 21, 26, 28, 32, and 41 for obviousness over Alli and Hirahara. In particular, neither Bagga nor Kim, alone or in combination, overcomes the above-noted deficiencies of Alli and Hirahara.

In addition, Applicants disagree that the utilization of a carrier for storage proteins, or as a fusion protein, constitutes an obvious modification. As noted previously, by inserting a hybrid peptide as presently claimed, on the order of 70 to 175, more preferably 84 to 133 amino acids in length, into a glutelin variable region and expressing it, the protein gets accumulated in PB-I as a glutelin precursor. This is particularly advantageous in the context of

inducing immune tolerance, wherein glutelin is produced as a precursor, and is processed after being transported to PB-2, which is where glutelin is conventionally accumulated, and is then digested into an acid subunit and a basic subunit. By inserting the epitope, it gets accumulated as a precursor, which, in turn, affords it with novel and unexpected advantages over the prior art, such advantages serving as further indicia of non-obviousness.

For all the above reasons, the rejection of claims 6, 27, and 29 for obviousness over Alli in view of Hirahara, Bagga, and Kim is improper and should be withdrawn.

In view of all of the foregoing, Applicants submit that this case is in condition for allowance and such allowance is earnestly solicited.

Respectfully submitted,

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